Role of the PI3K/AKT signaling pathway in regulating gene expression in rheumatoid arthritis (Review)

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Abstract. Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation and joint destruction. As the disease progresses, joint deformity, loss of joint function and disability may occur, thereby seriously affecting the quality of life of patients, as well as their physical and mental health. The PI3K/AKT signaling pathway serves a critical role in regulating inflammatory responses, cell survival and gene expression in RA. The present review aimed to summarize how PI3K/AKT modulates the expression of key genes involved in RA pathogenesis, including cytokines and non-coding RNAs. In addition, the crosstalk between PI3K/AKT and other signaling pathways, as well as the potential therapeutic strategies currently available for RA, are discussed.

Contents

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1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterized by persistent synovitis, progressive cartilage degradation and bone erosion, which over time leads to severe joint impairment and disability (1,2). Although the age-adjusted prevalence of RA is ~1% worldwide, it remains a major contributor to healthcare expenditure, particularly in the context of global population aging (3,4). The etiology of RA is multifactorial and has been attributed to a combination of genetic susceptibility, environmental triggers and dysregulated immune responses, which together lead to the overactivation of various immune cells and, notably, drive fibroblast-like synoviocytes (FLSs) toward an invasive and anti-apoptotic phenotype, ultimately resulting in immune-mediated joint destruction and dysfunction (5,6).

Current therapeutic strategies for RA primarily aim to alleviate symptoms and slow disease progression. These strategies include non-steroidal anti-inflammatory drugs, glucocorticoids, and conventional synthetic or biologic disease-modifying antirheumatic drugs (7,8). Despite their clinical utility, a notable proportion of patients exhibit inadequate responses to these therapies, and long-term use is often associated with considerable adverse effects, including infections, hepatic toxicity and cardiovascular complications (9,10). Therefore, elucidating the intricate molecular mechanisms underlying RA pathogenesis remains imperative for identifying novel therapeutic targets, and developing more effective and safer treatment modalities.

Among the numerous signaling pathways involved in RA, the NF-κB pathway has been the most extensively studied because of its role in mediating inflammation (11,12). Nonetheless, accumulating evidence has highlighted the crucial role of the PI3K/AKT signaling axis as a key inflammatory regulator in RA, controlling not only inflammation, but also cell survival, proliferation and metabolism (13). The PI3K/AKT signaling pathway is activated by various cytokines and growth factors in the RA synovial microenvironment. Once activated, this pathway exerts profound effects on gene regulatory networks involved in pathological processes; it modulates the activity of downstream transcription factors, such as NF-κB, and regulates

the expression of pro-inflammatory cytokines (14). The present study hypothesizes that pathological alterations in the PI3K/AKT pathway affect multiple cellular functions, modulate immune responses, and contribute to persistent synovitis and joint destruction by regulating the expression of pro-inflammatory cytokines (for example, TNF-α, IL-1β and IL-6), matrix metalloproteinases (MMPs) and anti-apoptotic proteins (15,16).

Additionally, regulation of the PI3K/AKT pathway is closely associated with non-coding RNAs (ncRNAs), which have been recognized as important epigenetic regulators of gene expression in RA (17-19). The interaction between ncRNAs and signaling pathways adds a further layer of complexity to the regulation of gene expression in RA.

Although the role of NF-κB in RA has been well described, to the best of our knowledge, a systematic review focusing on the PI3K/AKT signaling pathway and its complex regulatory effects on gene expression in RA is still lacking. Specifically, existing reviews (11,12) have often discussed the PI3K/AKT pathway alongside other signaling pathways without emphasizing its distinct role in gene expression regulation, or they have failed to clearly distinguish between general PI3K/AKT biology and RA-specific evidence. The present review aimed to fill this gap by providing a focused synthesis of how PI3K/AKT modulates gene expression in RA, with a clear distinction between established findings in RA tissues and cells, and indirect evidence derived from other disease models. To ensure transparency and reproducibility, the present study conducted a narrative review based on a systematic literature search of PubMed (pubmed.ncbi.nlm.nih.gov) and Web of Science (https://www.webofscience.com) covering the period January 2000-December 2025, using the key words 'PI3K/AKT', 'rheumatoid arthritis', 'gene expression' and 'non-coding RNA'. Studies were included if they addressed PI3K/AKT signaling in RA or related inflammatory arthritis models; mechanistic studies from non-RA contexts were used only as background support for general pathway biology and were explicitly identified as such. The present study aimed to summarize the PI3K/AKT signaling pathway and its mechanisms of activation, its central role in regulating the expression of genes involved in RA pathology, and its dynamic crosstalk with other signaling pathways and ncRNAs. Finally, we address the therapeutic potential of targeting the PI3K/AKT axis and emerging ncRNA-based strategies for the future management of RA.

2. PI3K/AKT signaling pathway in RA

The PI3K/AKT signaling pathway is a critical intracellular signaling cascade that regulates a wide range of cellular processes, including metabolism, proliferation, survival and inflammation. Its aberrant activation is increasingly recognized as a cornerstone of the pathogenic mechanisms underlying RA (20,21).

Pathway components and activation mechanisms. PI3Ks are heterodimeric enzymes composed of a regulatory subunit and a catalytic (p110) subunit. They are classified into different classes, among which class IA PI3Ks (p110α, p110β and p110δ) are primarily activated by receptor tyrosine kinases upon stimulation by growth factors and cytokines, whereas class IB PI3K (p110γ) is activated by G-protein-coupled receptors (GPCRs), such as chemokine receptors (22,23). These general activation mechanisms have been well established in various cell types; in the context of RA, they are mainly supported by studies involving RA-derived FLSs and immune cells.

A key feature of PI3K activation is its potentiation by Ras family GTPases. Once activated, PI3K phosphorylates phosphatidylinositol lipids at the plasma membrane, thereby generating docking sites for proteins containing pleckstrin homology domains, most notably phosphoinositide-dependent kinase 1 (PDK1) and AKT (24). The tumor suppressor PTEN serves as the primary negative regulator of this pathway by dephosphorylating these lipid intermediates (25). AKT functions as the central node of PI3K signaling, and its phosphorylation by PDK1 and mammalian target of rapamycin complex (mTORC)2 results in full activation. Downstream, AKT coordinates cellular responses by phosphorylating and modulating the activity of numerous substrates, including inhibitor of κB kinase (IKK), the pro-apoptotic protein Bad, glycogen synthase kinase-3β (GSK-3β), mTOR and forkhead box O (FoxO) transcription factors (26,27).

Aberrant PI3K/AKT activation in the RA synovium. There is evidence for constitutive activation of the PI3K/AKT axis in the RA synovial microenvironment (15). One line of evidence comes from the reduced expression of PTEN mRNA in the invasive layer of the RA synovium, a specific sublayer within the synovial lining, as well as in FLSs invading cartilage in a murine arthritis model (28). Loss of this negative regulator supports hyperactivation of the pathway. Consistent with this, levels of phosphorylated-AKT are markedly increased in RA synovial tissue and purified FLSs compared with specimens from patients with osteoarthritis or healthy controls (29). Functionally, pro-inflammatory cytokines, such as TNF-α, potently activate AKT in RA-FLSs *in vitro*. Inhibition of PI3K by LY294002 or overexpression of PTEN sensitizes these cells to TNF-α-induced apoptosis, demonstrating that the PI3K/AKT pathway provides a survival signal that contributes to the apoptosis-resistant phenotype of RA-FLSs (30,31). Moreover, this pathway mediates resistance to cell death induced by other cytokines, such as TNF-related apoptosis-inducing ligand (32). These findings help explain the dual role of the PI3K/AKT pathway in promoting both synovial hyperplasia and inflammation. Most of these observations are derived from direct studies of RA tissues and FLSs (28-32), thus providing disease-specific evidence. The mechanistic details regarding Ras-mediated PI3K activation are derived mainly from studies non-RA systems (24,33). As direct validation in RA tissues remains limited, these findings should be interpreted as general PI3K/AKT pathway biology rather than RA-specific evidence. Fig. 1 presents a comprehensive schematic diagram of the PI3K/AKT signaling pathway in the pathogenesis of RA.

3. Regulation of gene expression via PI3K/AKT

Gene expression in RA is regulated by the PI3K/AKT pathway through a series of interconnected mechanisms, including, but not limited to, inflammatory responses, synovial cell survival and maintenance of joint structural integrity (13-15). The present review distinguishes between evidence derived directly from RA tissues and cells [for example, human RA synovium, RA-FLSs and collagen-induced arthritis (CIA)

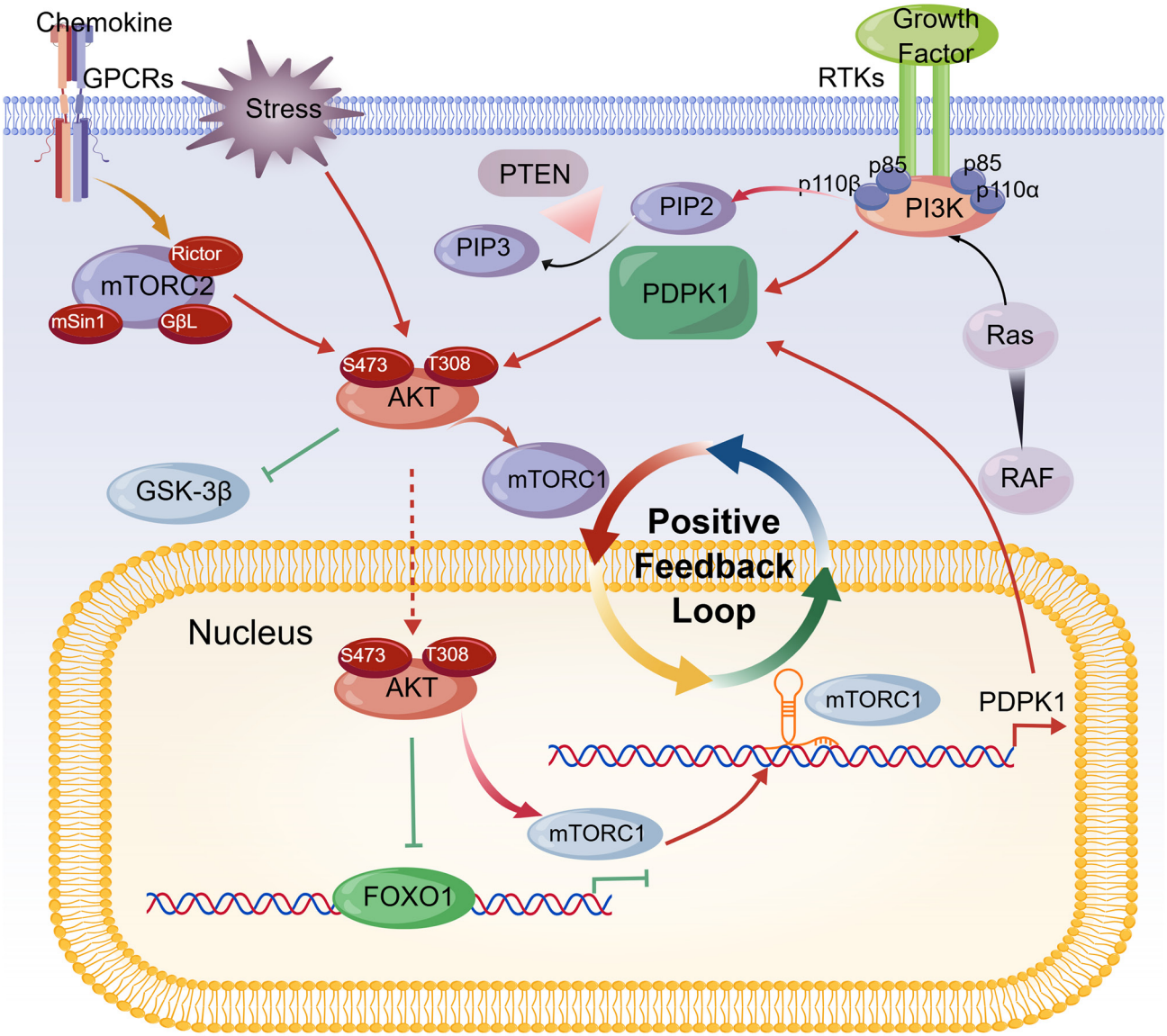

Figure 1. Schematic diagram of the PI3K/AKT signaling pathway in the pathogenesis of rheumatoid arthritis. Upstream activators, including growth factors and chemokines, act through RTKs and GPCRs to activate class IA and class IB PI3K, leading to the conversion of PIP2 to PIP3, a process antagonized by PTEN. Downstream activation of AKT regulates cell proliferation and immune inflammation through multiple effectors, including the Ras/RAF/MEK/ERK and mTOR pathways. FOXO1, Forkhead box O1; GPCR, G-protein-coupled receptor; GSK-3β, Glycogen synthase kinase-3β; mTORC1, Mammalian target of rapamycin complex 1; PDPK1, 3-phosphoinositide-dependent protein kinase 1; PIP2, Phosphatidylinositol 4,5-bisphosphate; PIP3, Phosphatidylinositol 3,4,5-trisphosphate; RTK, Receptor tyrosine kinase. Created with BioGDP.com (104).

models] and weaker or indirect evidence from non-RA settings (for example, cancer, cardiac or brain injury studies), which is used only to suggest plausible mechanisms requiring further validation in RA.

Transcriptional regulation via downstream effectors. Once activated, AKT phosphorylates a series of transcription factors and regulatory proteins that modulate gene expression profiles in RA synovial cells. Among these, the NF-κB pathway represents one of the most important downstream effectors. Phosphorylation and activation of IKK lead to the phosphorylation of IκB, resulting in its degradation and the subsequent nuclear translocation of NF-κB (34,35). This, in turn, enhances the transcription of pro-inflammatory genes, including TNF-α, IL-1β, IL-6 and IL-8, as well as MMPs, such as MMP-3 and MMP-9, which have critical roles in synovitis and cartilage degradation (36,37). Moreover, AKT-mediated phosphorylation of FoxO transcription factors leads to their cytoplasmic sequestration and inactivation, thereby suppressing the expression of pro-apoptotic genes such as Bim and FasL (Fig. 2). This mechanism contributes to the apoptosis-resistant phenotype of FLSs in RA (38,39). In addition, mTOR is another major downstream substrate of AKT. Activation of mTORC1 positively regulates mRNA translation and the expression of proteins involved in cell proliferation and metabolism through phosphorylation of ribosomal protein S6 kinase 1 and eukaryotic translation initiation factor 4E-binding protein 1 (40-42). This promotes the synthesis of cyclins, MMPs and inflammatory mediators, thereby enhancing synovial proliferation and inflammation. All of the aforementioned mechanisms have been directly demonstrated in RA-FLSs or RA synovial tissues, representing strong disease-specific evidence.

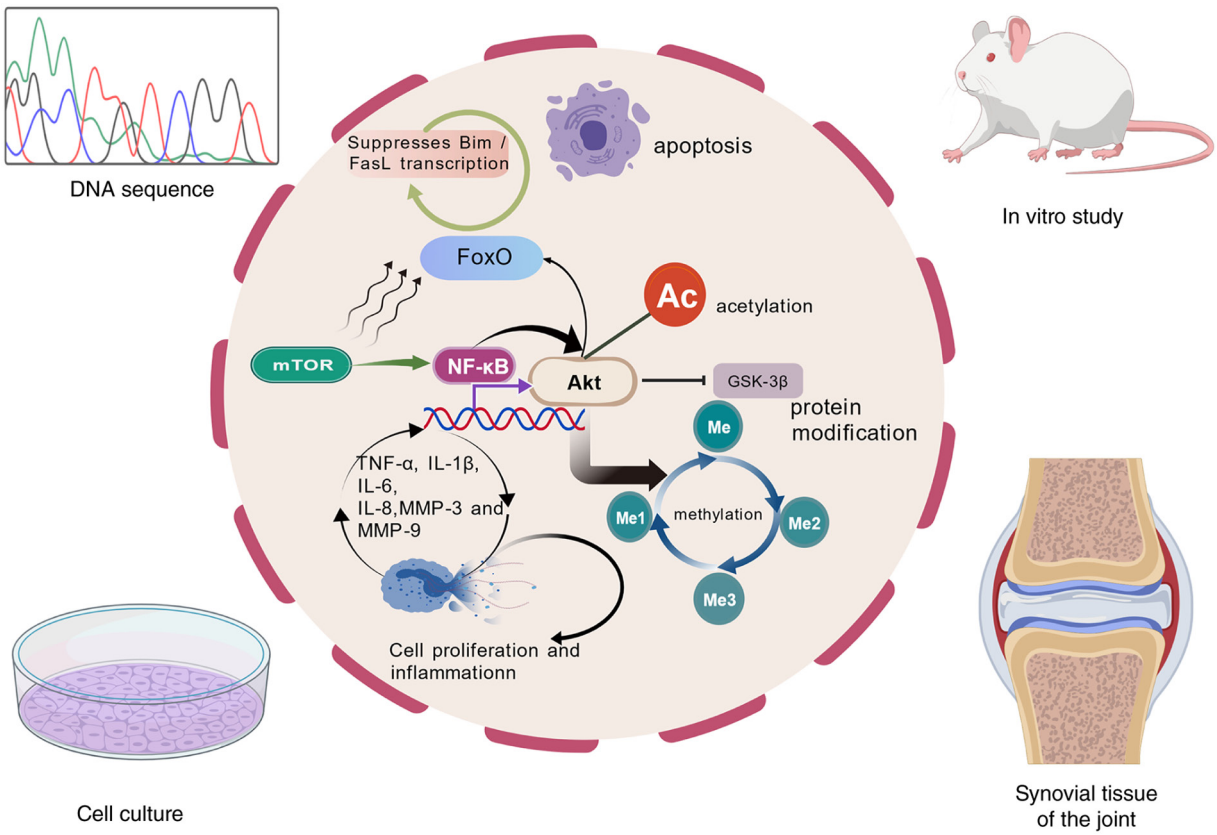

Figure 2. Post-transcriptional and epigenetic modification mechanisms of the PI3K/AKT pathway in rheumatoid arthritis. This diagram illustrates how activated AKT modulates transcription factors and downstream effectors, including NF-κB, FoxO, mTOR and GSK-3β, to regulate the expression of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6 and IL-8, as well as MMPs (MMP-3 and MMP-9), thereby promoting cell proliferation and inflammation. FoxO, Forkhead box O; GSK-3β, Glycogen synthase kinase-3β; Created with BioGDP.com (104).

Post-transcriptional and epigenetic mechanisms. In addition to its role in transcriptional control, the PI3K/AKT pathway can influence gene expression through post-transcriptional and epigenetic mechanisms. AKT activation may stabilize specific mRNAs by inhibiting GSK-3β (Fig. 2), which is considered to mediate mRNA decay (43). In addition, PI3K/AKT signaling can induce epigenetic changes, such as histone acetylation and DNA methylation, thereby remodeling chromatin and altering gene expression in RA-FLSs (Fig. 2). For example, AKT activation has been associated with increased histone H3 acetylation at the promoters of inflammatory genes, thereby facilitating their transcription (44,45). These epigenetic observations are primarily based on *in vitro* studies of RA-FLSs; however, the direct link between AKT and specific histone modifications in RA synovium *in vivo* remains less well established and warrants further investigation. Fig. 2 presents a schematic diagram of the transcriptional and epigenetic regulation mediated by the PI3K/AKT signaling pathway.

Cross-talk with ncRNAs. A critical layer of regulation of PI3K/AKT signaling is provided by ncRNAs. Multiple microRNAs (miRNAs/miRs) have been shown both to regulate and to be regulated by PI3K/AKT signaling. In particular, miR-124a directly targets the p110α catalytic subunit of PI3K (encoded by PIK3CA), thereby inhibiting AKT activation and downstream NF-κB signaling (Fig. 3). This leads to suppression of RA-FLS proliferation and reduced production of inflammatory cytokines (19). By contrast, miR-21 is upregulated in the RA synovium and promotes PI3K/AKT activation by suppressing PTEN (Fig. 3), thereby enhancing FLS survival and inflammation (46,47).

Notably, long ncRNAs (lncRNAs) are key modulators of the PI3K/AKT pathway in RA. For example, the lncRNA THRIL is upregulated in the serum of patients with RA, and knockdown of THRIL in TNF-α-stimulated RA-FLSs reduces the phosphorylation of PI3K and AKT, concomitantly decreases the production of IL-1β and MMP-3 and promotes apoptosis (48) (Fig. 3). These findings suggest that THRIL exerts its pro-inflammatory and anti-apoptotic effects, at least in part, through activation of the PI3K/AKT pathway. Similarly, the lncRNA H19 has been shown to promote AKT phosphorylation by serving as a competing endogenous RNA (ceRNA) for miRNAs that target AKT regulators; for example, H19 acts as a ceRNA to modulate the PI3K/AKT pathway (49,50), thereby promoting inflammatory responses (Fig. 3).

Circular RNAs (circRNAs) also participate in this regulatory network. For example, circRNA_09505 sponges miR-6089 (Fig. 3), thereby relieving its suppression of AKT1 mRNA, which leads to enhanced AKT signaling and aggravated inflammation in RA macrophages (51).

All ncRNA examples discussed in the present review are derived from samples of patients with RA or RA-FLS models, thus representing direct evidence in RA. Fig. 3 presents a

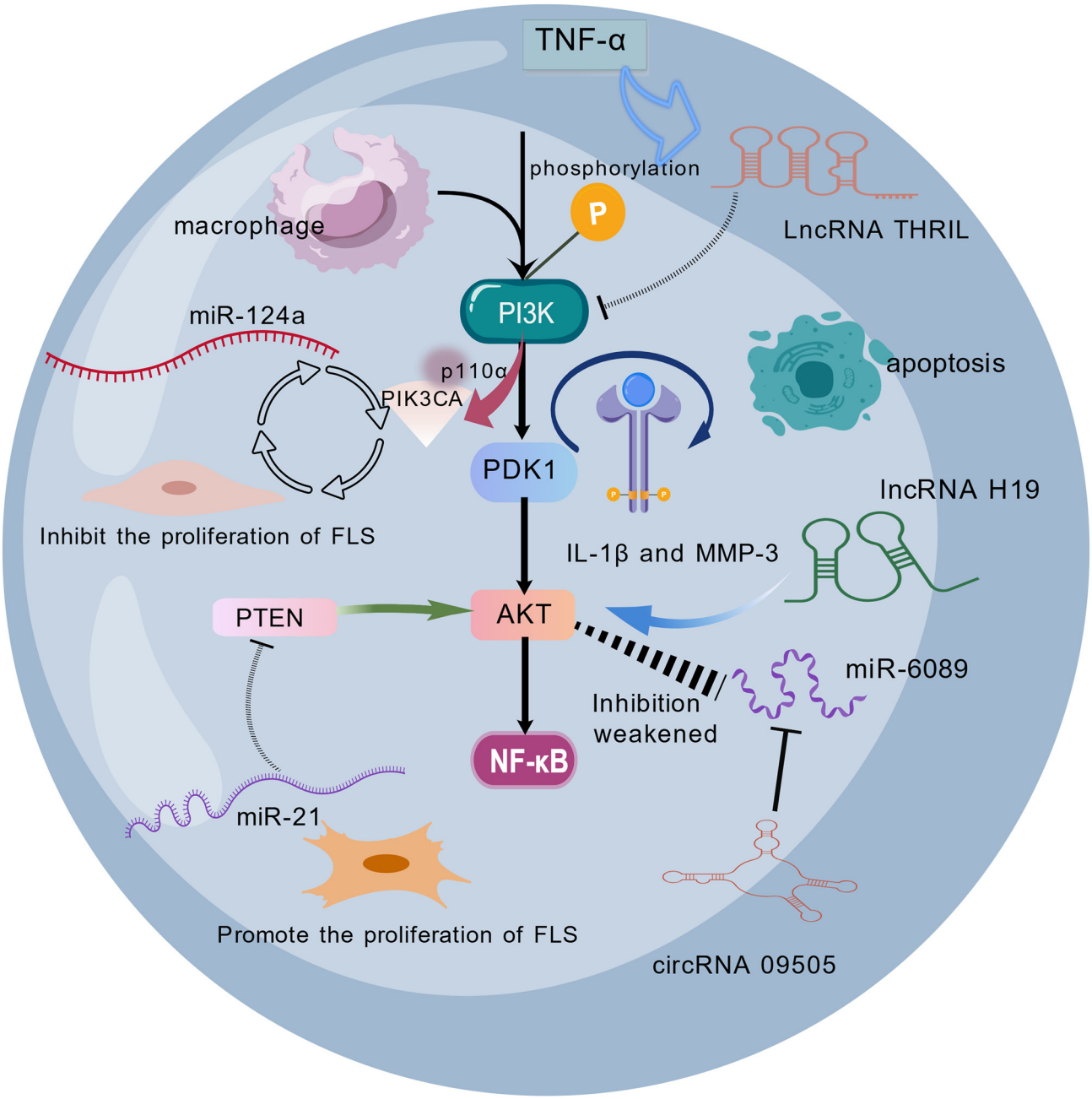

Figure 3. Crosstalk between the PI3K/AKT signaling pathway and ncRNAs in rheumatoid arthritis. ncRNAs, including miR-124a, miR-21, lncRNA THRIL, lncRNA H19 and circRNA_09505, modulate PI3K/AKT signaling at multiple levels. miR-124a directly targets the PI3K p110α subunit (PIK3CA) to inhibit FLS proliferation, whereas miR-21 suppresses PTEN to promote FLS proliferation. lncRNA THRIL activates PI3K/AKT signaling, thereby increasing IL-1β and MMP-3 expression levels; lncRNA H19 functions as a competing endogenous RNA; and circRNA_09505 sponges miR-6089 to enhance AKT1 expression in macrophages. circRNA, circular RNA; FLS, fibroblast-like synoviocyte; lncRNA, long ncRNA; miR, microRNA; PDK1, phosphoinositide-dependent kinase 1.Created with BioGDP.com (104).

schematic diagram of the crosstalk between the PI3K/AKT signaling pathway and ncRNAs.

4. Crosstalk with other pathways

The pathogenesis of RA is not governed by isolated signaling cascades, but rather by a highly interconnected network of pathways that amplify and sustain inflammatory and destructive processes. Although the PI3K/AKT pathway serves a central role, it does not function in isolation; instead, it engages in extensive crosstalk with other key signaling axes, thereby orchestrating a synergistic amplification of pro-inflammatory gene expression and synovial pathology.

Crosstalk with the NF-κB pathway. The interaction between PI3K/AKT and NF-κB is arguably the most understood among these signaling networks. AKT directly phosphorylates and activates IKK, thereby promoting IκB degradation and the nuclear translocation of NF-κB. In this way, it facilitates the increased expression of various pro-inflammatory genes, including TNF-α, IL-1β, IL-6 and MMPs (52,53). This mechanism has been repeatedly validated in RA-FLSs

and animal models of RA, providing strong direct evidence. Conversely, NF-κB can further enhance PI3K/AKT signaling by upregulating cytokines such as IL-6, which promote the activation of upstream receptor tyrosine kinases and GPCRs, thereby creating a positive feedback loop that sustains chronic inflammation and drives RA progression (54).

Interaction with the JAK/STAT pathway. The JAK/STAT pathway represents another important inflammatory signaling pathway in RA. Cytokine receptors associated with JAKs can also recruit and activate PI3K through phosphorylated tyrosine residues, thereby leading to downstream AKT activation (55,56). This interaction has been demonstrated in RA-FLSs and synovial tissues. In addition, STAT3, the principal transducer of IL-6 signaling, transcriptionally upregulates genes involved in cell survival and inflammation that are also modulated by AKT, such as Bcl-2 and MMP-9 (57,58). This overlap suggests that combined inhibition of the JAK/STAT and PI3K/AKT pathways may produce synergistic therapeutic effects, as indicated by preclinical and clinical studies of dual-pathway inhibition (59,60).

Interplay with MAPK signaling. In RA, the MAPK pathway, including ERK and p38, frequently exhibits cross-activation with PI3K/AKT signaling. For example, AKT antagonizes apoptosis signal-regulating kinase 1 (ASK1), an upstream activator of p38 and JNK, thereby influencing stress-induced apoptosis and inflammation (61,62). However, much of the evidence for the interaction between AKT and ASK1 is derived from non-RA contexts, such as cancer and neurotoxicity models (61,62), and direct validation in RA remains limited. Meanwhile, MAPK activation can also influence PI3K signaling through ribosomal S6 kinase-mediated phosphorylation of AKT or by increasing the expression of growth factors that activate PI3K (63,64). This bidirectional crosstalk further underscores that targeting a single pathway in isolation may be insufficient, and that multi-target therapeutic strategies may be required.

Modulation by Notch signaling. Evidence indicates that Notch signaling modulates PI3K/AKT activity in RA. The Notch intracellular domain (NICD) can transcriptionally upregulate PIK3CA expression or inhibit PTEN, thereby enhancing AKT phosphorylation (65,66). These findings are supported by studies in RA synovial fibroblasts and animal models (65,66). In turn, AKT can stabilize NICD and enhance its transcriptional activity, thereby forming another positive feedback loop that promotes synovial cell survival and inflammatory cytokine production (67). Inhibition of Notch signaling has been shown to reduce AKT activation and ameliorate arthritis in animal models, suggesting that this pathway may represent a viable therapeutic target (68). Notch signaling via the NICD/CSL/Hey/DTX axis also promotes the invasive migration of RA-FLSs, a key feature of synovial hyperplasia and joint destruction (Fig. 4).

Integration with purinergic and inflammasome pathways. The P2X7R/NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome axis also intersects with PI3K/AKT signaling. ATP-mediated activation of P2X7R can stimulate PI3K/AKT signaling, which in turn enhances NLRP3 inflammasome assembly and IL-1β maturation (69,70). These observations are primarily derived from non-RA models, such as brain injury (69) and a colorectal cancer model (70); however, recent studies in RA have begun to explore this link (71,72). Moreover, AKT-mediated activation of NF-κB primes NLRP3 expression, thereby completing a pro-inflammatory circuit that links purinergic signaling with cytokine release and synovitis (73,74). Targeting P2X7R or NLRP3 may therefore indirectly attenuate PI3K/AKT signaling. However, direct evidence for this crosstalk in RA remains preliminary and requires further investigation. Additionally, the PI3K/AKT pathway may contribute to apoptosis resistance and inflammation through its interplay with DNA damage response proteins. For example, DTX3L (also known as ARTD9), which is involved in the DNA damage response, has been shown to promote inflammation in RA-FLSs by increasing STAT1 translocation (75). This crosstalk represents a promising area for future investigation into the mechanisms driving the anti-apoptotic and pro-inflammatory phenotype of RA-FLSs (Fig. 4).

5. Therapeutic implications

Pharmacological inhibition of PI3K/AKT. Several small-molecule inhibitors targeting PI3K or AKT have shown promise in preclinical models of RA. For example, the PI3K inhibitor LY294002 and the AKT inhibitor MK-2206 have been shown to induce apoptosis in RA-FLSs, and reduce the production of pro-inflammatory cytokines and MMPs *in vitro* (76,77). Isoform-specific inhibitors, particularly those targeting PI3Kδ and PI3Kγ, are of particular interest because of their predominant expression in leukocytes and their roles in immune cell activation. Idelalisib, a PI3Kδ inhibitor approved for hematological malignancies, has shown efficacy in reducing disease severity by attenuating B-cell and macrophage activation (78,79). Similarly, duvelisib, a dual PI3Kδ/γ inhibitor, has been reported to suppress synovitis and bone erosion in animal models of RA by impairing neutrophil and macrophage migration into the joints (80).

Moreover, mTOR inhibitors such as rapamycin (sirolimus) and everolimus, which target a downstream effector of AKT, have also been evaluated in RA (81,82). Rapamycin has been reported to reduce synovial hyperplasia and the production of inflammatory cytokines in a review, suggesting that it may serve as a potential therapeutic target for RA (83). However, the clinical translation of these agents has been limited by systemic toxicity and off-target effects, highlighting the need for more selective and tissue-specific therapeutic strategies.

ncRNA-based therapeutic strategies. The regulatory role of ncRNAs in the PI3K/AKT pathway offers options for therapeutic intervention. For example, miR-124a, which targets PIK3CA, is downregulated in the RA synovium. Restoration of miR-124a expression through synthetic mimics or nanoparticle-based delivery systems has been shown to suppress PI3K/AKT/NF-κB signaling, inhibit FLS proliferation, and reduce inflammatory cytokine production *in vitro* and in CIA models (84). Similarly, a clinical study showed that miR-21 was markedly positively associated with RA disease activity,

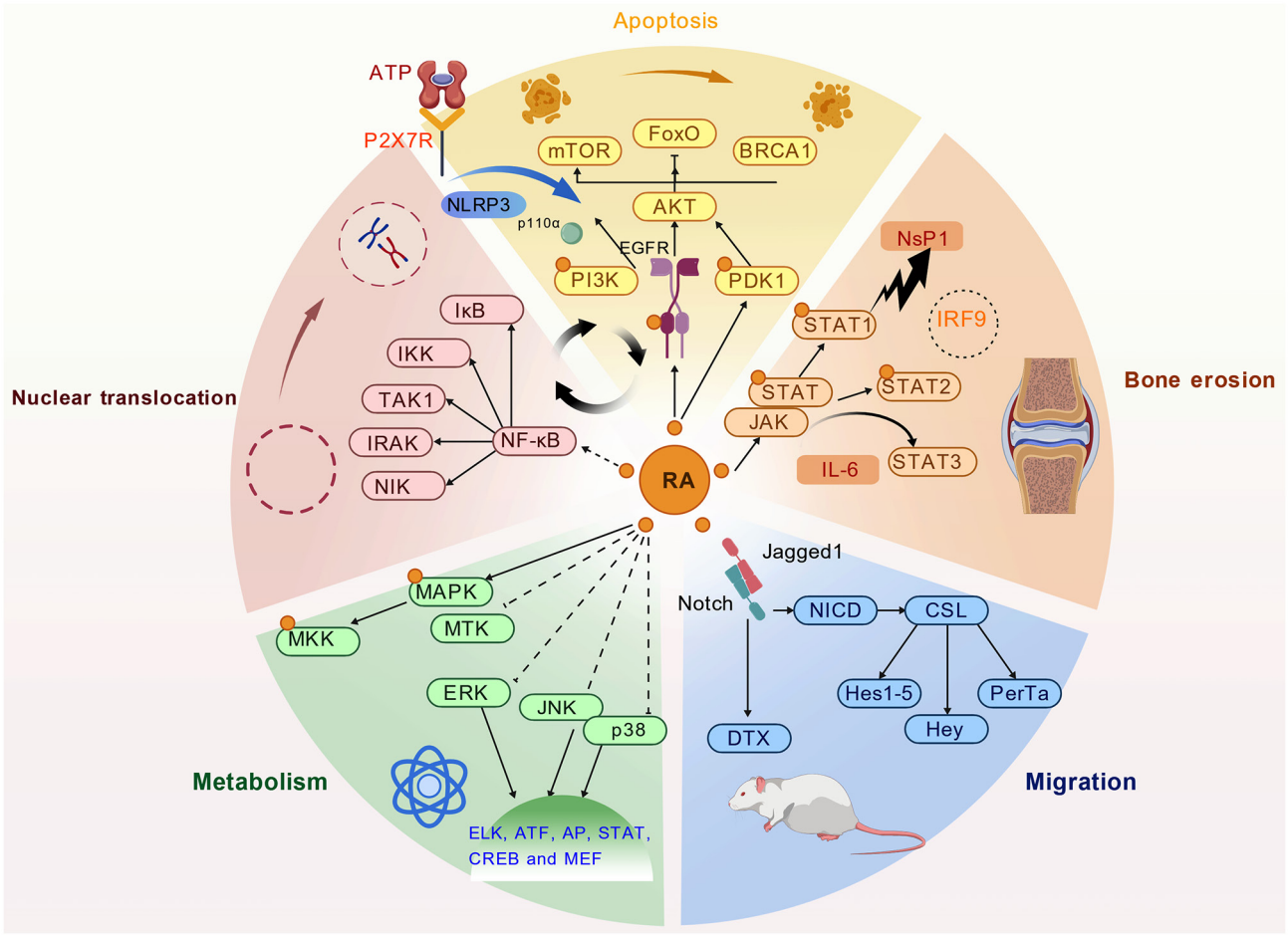

Figure 4. Integrated crosstalk between the PI3K/AKT signaling pathway and other key signaling pathways in RA. Interactions between PI3K/AKT and other major signaling pathways in RA, including apoptosis-related regulators (ATP/P2X7R, NLRP3, FoxO and BRCA1), inflammatory pathways (NF-κB, JAK/STAT and MAPK/ERK/JNK/p38), Notch signaling (NICD/CSL/Hey/DTX), and transcriptional outputs (ELK, ATF, AP, STAT, CREB and MEF). Together, these signaling networks contribute to bone erosion, metabolic alterations and cell migration in RA. FoxO, forkhead box O; IKK, inhibitor of κB kinase; NICD, Notch intracellular domain; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; PDK1, phosphoinositide-dependent kinase 1; RA, rheumatoid arthritis. Created with BioGDP.com (104).

indicating its potential value as a biomarker for future RA intervention (85). Targeting miR-21 may regulate the PI3K/AKT signaling pathway and slow RA progression (86). Qu *et al* (87) reported that overexpression of miR-126 in RA-FLSs inhibited PIK3R2 expression, while promoting proliferation and suppressing apoptosis. This finding suggests that inhibition of miR-126 may downregulate PI3K/AKT signaling and provide therapeutic benefits in RA.

lncRNAs and circRNAs also represent promising therapeutic targets. Silencing of lncRNA H19, which promotes AKT activation, using small interfering RNA (siRNA)- or CRISPR-based approaches has been shown to reduce inflammation and induce apoptosis in RA-FLSs (88). Wang and Liu (89) demonstrated through integrated computational and experimental analyses that regulation of the lncRNA DSCR9/RPLP2/PI3K/AKT axis may represent an important mechanism by which Xinfeng capsule improves the inflammatory response and hypercoagulable state in RA, and that lncRNA DSCR9 may serve as a potential therapeutic target. Liu *et al* (90) demonstrated, using an RA-FLS-induced human umbilical vein endothelial cell model, that lncRNA HOTAIR, as a potential therapeutic target in RA, can activate the PI3K/AKT pathway through the miR-126-3p/PIK3R2 regulatory axis, thereby promoting angiogenesis in RA. Likewise, circRNA_09505, which sponges miR-6089 and enhances AKT1 expression, promotes the production of TNF-α, IL-6 and IL-12 through a ceRNA mechanism, whereas knockdown of circRNA_09505 was shown to notably alleviate arthritis and inflammation in a CIA mouse model (51). These findings highlight the potential of RNA-based therapeutics to precisely modulate the PI3K/AKT axis, potentially with fewer off-target effects than broad-spectrum kinase inhibitors.

Combination therapies and pathway crosstalk. Due to the extensive crosstalk between PI3K/AKT and other signaling pathways, including NF-κB, JAK/STAT and MAPK, combination therapies targeting these pathways may achieve synergistic effects. For example, the co-administration of a PI3Kδ inhibitor and a JAK inhibitor (for example, tofacitinib) has been shown to suppress inflammatory cytokine production and synovial hyperplasia more effectively than either agent alone (91). Likewise, combined inhibition of PI3K and mTOR with agents such as dactolisib (BEZ235) has demonstrated greater efficacy in suppressing inflammatory activity (92).

Table I. Therapeutic strategies targeting the PI3K/AKT pathway in RA.

A, Pharmacological inhibition

Agent/approach	Mechanism of action	Experimental model	Key effects	(Refs.)
LY294002 (PI3K inhibitor)	Induces apoptosis in RA-FLSs; reduces pro-inflammatory cytokines and MMPs	RA-FLSs	Anti-proliferation, anti-inflammatory	(76,77)
MK-2206 (AKT inhibitor)	Induces apoptosis in RA-FLSs; reduces pro-inflammatory cytokines and MMPs	RA-FLSs	Anti-proliferation, anti-inflammatory	(76,77)
Idelalisib (PI3Kδ inhibitor)	Attenuates B cell and macrophage activation; reduces disease severity	*In vitro* and clinical trials	Immunosuppression, reduces synovial inflammation	(78,79)
Duvelisib (PI3Kδ/γ inhibitor)	Suppresses neutrophil/macrophage migration; reduces synovitis and bone erosion	RA animal models	Anti-proliferation, protects joint structure	(80)
Rapamycin (mTOR inhibitor)	Reduces synovial hyperplasia and cytokine production	-	Anti-proliferation, anti-inflammatory	(81,82)
Metformin	AMPK activation; indirectly suppresses the PI3K/AKT signaling pathway	RA-FLSs	Decreases disease activity	(95,96)
Triptolide	Inhibits the NF-κB, PI3K/AKT and p38 MAPK signaling pathways; modulates macrophage polarization	Adjuvant arthritis rat model	Improves immune imbalance and joint inflammation	(97)

B, ncRNA-based therapy

Agent/approach	Mechanism of action	Experimental model	Key effects	(Refs.)
miR-124a mimic	Targets PIK3CA; suppresses the PI3K/AKT/NF-κB signaling pathway	RA-FLSs	Reduces FLS proliferation and inflammation	(84)
Anti-miR-21 therapy	Regulates PI3K/AKT signaling; associated with RA disease activity	*In vitro* and clinical trials	Potential biomarker and therapeutic target	(85,86)
Anti-miR-126 therapy	Inhibits PIK3R2; promotes apoptosis, reduces proliferation	RA-FLSs	Pro-apoptotic, anti-proliferation	(87)
siRNA against lncRNA H19	Reduces AKT activation; induces apoptosis and reduces inflammation	RA-FLSs	Anti-inflammatory, pro-apoptotic	(88)
Targeting lncRNA DSCR9	Regulates the RPLP2/PI3K/AKT axis; improves inflammation and hypercoagulability	RA-PBMCs + RA-FLSs	Anti-inflammatory, anti-thrombotic	(89)
Targeting lncRNA HOTAIR	Activates PI3K/AKT via miR-126-3p/PIK3R2; promotes angiogenesis	RA-FLS-induced HUVEC model	Pro-angiogenic	(90)
siRNA against circRNA_09505	Sponges miR-6089; reduces AKT1 expression and cytokine production	Macrophage models and CIA models	Reduces arthritis severity and inflammation	(51)

C, Combination therapy

Agent/approach	Mechanism of action	Experimental model	Key effects	(Refs.)
PI3Kδ + JAK inhibitor	Suppression of cytokine production and synovial hyperplasia	-	Enhances anti-inflammatory and anti-proliferative effects	(91)

Table I. Continued.

PI3K + mTOR inhibitor	Dual pathway inhibition; reduces FLS survival and inflammation	*In vitro* animal model	Enhances efficacy in reducing inflammation	(92)

C, Combination therapy

Agent/approach	Mechanism of action	Experimental model	Key effects	(Refs.)
Curcumin + methotrexate	Inhibits the PI3K/AKT and NF-κB pathways; enhances anti-inflammatory effects	RA-FLSs, MH7A and CIA models	Synergistic anti-inflammatory	(93,94)

CIA, collagen-induced arthritis; circRNA, circular RNA; FLS, fibroblast-like synoviocyte; HUVEC, human umbilical vein endothelial cell; lncRNA, long ncRNA; miR, microRNA; ncRNA, non-coding RNA; PBMC, peripheral blood mononuclear cell; RA, rheumatoid arthritis; siRNA, small interfering RNA.

Natural compounds and repurposed drugs also offer multi-target potential. Curcumin, for example, has been shown to inhibit both the PI3K/AKT and NF-κB pathways, and its combination with methotrexate enhances anti-inflammatory effects in RA models (93,94). Metformin, an AMPK activator, indirectly suppresses PI3K/AKT signaling and has shown beneficial effects in decreasing disease activity in patients with RA (95,96). Wan *et al* (97) combined *in vitro* and *in vivo* experiments to demonstrate that triptolide can downregulate the expression of factors secreted by M1 macrophages, and inhibit the NF-κB, PI3K/AKT and p38 MAPK signaling pathways, thereby ameliorating immune imbalance, joint inflammation and tissue damage in RA. Table I summarizes the therapeutic strategies targeting the PI3K/AKT pathway in RA.

6. Discussion

The PI3K/AKT pathway is emerging as a key modulator of gene expression in RA and is involved in multiple pathological processes, ranging from inflammation to synovial hyperplasia and joint destruction. The present review compiled up-to-date evidence demonstrating the numerous, complex and occasionally conflicting roles of PI3K/AKT in RA, from its activation and downstream effects at the transcriptional and post-transcriptional levels to its dynamic interplay with other signaling pathways and ncRNAs.

The present study demonstrated that dysregulation of the PI3K/AKT pathway is a hallmark of the RA synovium, and is closely associated with both genetic and epigenetic alterations. Loss of PTEN, increased levels of phosphorylated-AKT and sustained activation of downstream effectors, such as mTOR and FoxO transcription factors, contribute to a pro-inflammatory and anti-apoptotic microenvironment. These changes promote the expression of key genes encoding cytokines, chemokines and matrix-remodeling enzymes, thereby driving disease activity.

It is also important to note that PI3K/AKT and ncRNAs form a complex, multilayered regulatory network. miR-124a and miR-21 are two notable regulators of the PI3K/AKT pathway, acting to suppress or enhance its activity, respectively. In addition, lncRNAs and circRNAs also participate in this regulatory system by functioning as molecular sponges or through direct interactions. These observations not only provide deeper insight into the pathogenesis of RA but also suggest new diagnostic and therapeutic opportunities.

Additionally, the extensive crosstalk between PI3K/AKT and other pathways, including NF-κB (52,54), JAK/STAT (56), MAPK (63), Notch (65,66) and inflammasome-related pathways (for example, nuclear pore complex, inhibitor of apoptosis protein 1 and receptor-interacting serine/threonine kinase 1) (69-72), reflects the pathophysiological complexity of RA. However, for some of these crosstalk mechanisms, particularly those involving MAPK and inflammasome pathways, the direct evidence in RA is less robust than that for NF-κB or JAK/STAT, and much of the current understanding has been extrapolated from non-RA models. Nevertheless, this extensive crosstalk argues against the sufficiency of targeted monotherapy for comprehensive disease control and suggests that combination strategies targeting multiple nodal points should be considered.

Although preclinical studies of small-molecule inhibitors and ncRNA-based therapeutics have shown considerable promise, several major translational barriers must be addressed before clinical application. First, toxicity remains a major concern: Broad PI3K inhibitors (for example, LY294002) and pan-AKT inhibitors are associated with notable systemic toxicities, including hyperglycemia, rash and immunosuppression, owing to the ubiquitous expression of PI3K/AKT in normal tissues (98). Isoform-selective inhibitors, such as PI3Kδ/γ inhibitors, may reduce some off-target effects, but they still carry risks of infection and hepatotoxicity (99,100). Second, selectivity remains a challenge, as achieving specific inhibition of pathogenic PI3K/AKT activity in synovial tissue without disrupting physiological signaling is difficult (101). Third, delivery represents a critical obstacle for ncRNA-based therapeutics, such as miRNA mimics, siRNA and anti-lncRNA agents, as efficient and stable delivery to inflamed joints with minimal off-target accumulation in the liver and kidneys is required. Current strategies include nanoparticle

encapsulation, exosome-based delivery and intra-articular administration, but none has yet been approved for clinical use in RA (102,103). Fourth, heterogeneity in patient responses must also be considered, as not all patients with RA exhibit the same degree of PI3K/AKT activation (60). Biomarkers, such as PTEN loss, phosphorylated-AKT levels and specific ncRNA signatures, are therefore needed to identify those patients most likely to benefit from PI3K/AKT-targeted therapies (84). These barriers are often underemphasized in preclinical studies, and rigorous evaluation in large-animal models and early-phase clinical trials is required before clinical translation.

Overall, the current review hypothesizes that therapeutic targeting of the PI3K/AKT axis holds considerable promise, as supported by preclinical studies of small-molecule inhibitors and ncRNA-based interventions. However, a number of mechanistic details, such as certain crosstalk pathways and some epigenetic modifications, are still based on indirect evidence from non-RA settings, and direct validation in RA tissues or animal models remains necessary. Future studies should therefore prioritize RA-specific mechanistic validation, the development of selective and safe inhibitors, and biomarker-driven clinical trials. More selective inhibitors and improved RNA-based therapeutics need to be developed, and biomarkers capable of identifying patients most likely to benefit from PI3K/AKT-targeted therapies should be established.

Overall, the PI3K/AKT pathway can be regarded as a major regulator of gene expression in RA, linking diverse signaling inputs to disease-relevant transcriptional programs. A comprehensive understanding of this pathway will be essential for the development of next-generation therapeutic strategies aimed at achieving sustained remission in RA.

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Authors' contributions

CC was involved in conceptualization, constructed figures and wrote, reviewed and edited the original draft. YW and JL wrote the manuscript and supervised. CJ reviewed the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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